


**INFORMATION DISCLOSURE
CITATION**

APPLN. NO.

10/537,545

ATTY. DKT. NO.

5192-16

APPLICANT

ZLOKOVIC et al.

FILING DATE

December 18, 2006

GROUP

1649

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	4,981,952	01/1991	Yan			
	5,321,123	06/1994	Griffin et al.			
	5,405,946	04/1995	Griffin et al.			
	5,663,142	09/1997	Bouma et al.			
	5,804,181	09/1998	Eibl et al.			
	5,891,843	04/1999	Turecek et al.			
	6,008,199	12/1999	Grinnell et al.			
	6,130,201	10/2000	Croce et al.			
	6,756,208	06/2004	Griffin et al.			
	7,204,981	04/2007	Ciaccia et al.			
	7,498,305	03/2009	Griffin et al.			
	2003/0073632	04/2003	Ciaccia et al.			
	2004/0132688	07/2004	Griffin et al.			
	2005/0037964	02/2005	Griffin et al.			
	2007/0042961	02/2007	Griffin et al.			
	2007/0142272	06/2007	Zlokovic et al.			
	2007/0142293	06/2007	Ciaccia et al.			
	2008/0305100	12/2008	Zlokovic et al.			

FOREIGN PATENT DOCUMENTS

DOCUMENT	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO
93/09807	05/1993	WO			
01/56532	08/2001	WO			
2004/030619	04/2004	WO			
2004/056309	07/2004	WO			
2005/007820	01/2005	WO			
2006/014839	02/2006	WO			
2008/055145	05/2008	WO			

OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)

	Abraham et al. "Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: A multicenter, randomized, placebo-controlled, single-blind, dose escalation study" <i>Crit. Care Med.</i> 29:2081-2089 (2001)
	Arosio et al. "Mutation of W215 compromises thrombin cleavage of fibrinogen, but not of PAR-1 or protein C" <i>Biochemistry</i> 39:8095-8101 (2000)
	Balazs et al. "Endothelial protein C receptor (CD201) explicitly identifies hematopoietic stem cells in murine bone marrow" <i>Blood</i> 107:2317-2321 (2006)
	Berg et al. "Engineering the proteolytic specificity of activated protein C improves its pharmacological properties" <i>Proc. Natl. Acad. Sci. USA</i> 100:4423-4428 (2003)
	Bernard et al. "Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis" <i>Crit. Care Med.</i> 29:2051-2059 (2001)
	Bernard et al. "Efficacy and safety of recombinant human activated protein C for severe sepsis" <i>New Engl. J. Med.</i> 344:699-709 (2001)

*Examiner

Date Considered

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OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)

	Chase & Shaw "p-Nitrophenyl-p'-guanidinobenzoate HCl: A new active site titrant for trypsin" <i>Biochem. Biophys. Res. Comm.</i> 29:508-514 (1967)
	Cheng et al. "Activated protein C inhibits tissue plasminogen activator-induced brain hemorrhage" <i>Nature Med.</i> 12:1278-1285 (2006)
	Conway et al. "The lectin-like domain of thrombomodulin confers protection from neutrophil-mediated tissue damage by suppressing adhesion molecule expression via nuclear factor κB and mitogen-activated protein kinase pathways" <i>J. Exp. Med.</i> 196:565-577 (2002)
	Edgell et al. "Permanent cell line expressing human factor VIII-related antigen established by hybridization" <i>Proc. Natl. Acad. Sci. USA</i> 80:3734-3737 (1983)
	Esmon "The anticoagulant and anti-inflammatory roles of the protein C anticoagulant pathway" <i>J. Autoimmun.</i> 15:113-116 (2000)
	Esmon "Regulation of blood coagulation" <i>Biochim. Biophys. Acta</i> 1477:349-360 (2000)
	Esmon "The endothelial cell protein C receptor" <i>Thromb Haemost.</i> 83:639-643 (2000)
	Esmon "Protein C pathway in sepsis" <i>Ann. Med.</i> 34:598-605 (2002)
	Feistritzer et al. "Protective signaling by activated protein C is mechanistically linked to protein C activation on endothelial cells" <i>J. Biol. Chem.</i> 281:20077-20084 (2006)
	Fisher et al. "Models of the serine protease domain of the human antithrombotic plasma factor activated protein C and its zymogen" <i>Protein Sci.</i> 3:588-599 (1994)
	Friedrich et al. "Secondary substrate-binding exosite in the serine protease domain of activated protein C important for cleavage at Arg-506 but not at Arg-306 in factor Va" <i>J. Biol. Chem.</i> 276:23105-23108 (2001)
	Friedrich et al. "Structural and energetic characteristics of the heparin-binding site in antithrombotic protein C" <i>J. Biol. Chem.</i> 276:24122-24128 (2001)
	Fukudome & Esmon "Molecular cloning and expression of murine and bovine endothelial cell protein C/activated protein C receptor (EPCR). The structural and functional conservation in human, bovine, and murine EPCR" <i>J. Biol. Chem.</i> 270:5571-5577 (1995)
	Gale et al. "Nonenzymatic anticoagulant activity of the mutant serine protease Ser360Ala-activated protein C mediated by factor Va" <i>Protein Sci.</i> 6:132-140 (1997)
	Gale et al. "The autolysis loop of activated protein C interacts with factor Va and differentiates between the Arg506 and Arg306 cleavage sites" <i>Blood</i> 96:585-593 (2000)
	Gale et al. "Molecular characterization of an extended binding site for coagulation factor Va in the positive exosite of activated protein C" <i>J. Biol. Chem.</i> 277:28836-28840 (2002)
	Gerlitz & Grinnell "Mutation of protease domain residues Lys37-39 in human protein C inhibits activation by the thrombomodulin-thrombin complex without affecting activation by free thrombin" <i>J. Biol. Chem.</i> 271:22285-22288 (1996)
	Griffin et al. "Activated protein C: Potential therapy for severe sepsis, thrombosis, and stroke" <i>Semin. Hematol.</i> 39:197-205 (2002)
	Griffin et al. "The promise of protein C" <i>Blood Cells</i> 36:211-216 (2006)
	Griffin et al. "Activated protein C" <i>J. Thromb. Haemost.</i> 5:73-80 (2007)
	Grinnell et al. "Differentiation of cytoprotective vs. anticoagulant function with variants of activated protein C in LPS-induced renal microvascular dysfunction" <i>Crit. Care Med.</i> 35(suppl.):A11, abstract 42 (2007)
	Grotta et al. "Adding to the effectiveness of intravenous tissue plasminogen activator for treating acute stroke" <i>Circulation</i> 107:2769-2770 (2003)
	Guo et al. "Species-dependent neuroprotection by activated protein C mutants with reduced anticoagulant activity" <i>J. Neurochem.</i> 109:116-124 (2009)
	Haley et al. "The activation of bovine protein C by factor Xa" <i>J. Biol. Chem.</i> 264:16303-16310 (1989)

*Examiner

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1649

OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)

	Han et al. "Proteomic analysis of active multiple sclerosis lesions reveals therapeutic targets" <i>Nature</i> 451:1076-1081 (2008)
	Heeb et al. "Inhibition of activated protein C by recombinant α_1 -antitrypsin variants with substitution of arginine or leucine for methionine ³⁵⁸ " <i>J. Biol. Chem.</i> 265:2365-2369 (1990)
	Hinds "Treatment of sepsis with activated protein C" <i>Brit. Med. J.</i> 323:881-882 (2001)
	Hotchkiss et al. "The pathophysiology and treatment of sepsis" <i>N. Engl. J. Med.</i> 348:138-150 (2003)
	Idziorek et al. "YOPRO-1 permits cytofluorometric analysis of programmed cell death (apoptosis) without interfering with cell viability" <i>J. Immunol. Meth.</i> 185:249-258 (1995)
	Isobe et al. "Activated protein C prevents endotoxin-induced hypotension in rats by inhibiting excessive production of nitric oxide" <i>Circulation</i> 104:1171-1175 (2001)
	Joyce et al. "Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis" <i>J. Biol. Chem.</i> 276:11199-11203 (2001)
	Kalafatis & Mann "Role of the membrane in the inactivation of factor Va by activated protein C" <i>J. Biol. Chem.</i> 268:27246-27257 (1993)
	Kanji et al. "Recombinant human activated protein C, drotrecogin alfa (activated): A novel therapy for severe sepsis" <i>Pharmacother.</i> 21:1389-1402 (2001)
	Kerschen et al. "Endotoxemia and sepsis mortality reduction by non-anticoagulant activated protein C" <i>J. Exp. Med.</i> 204:2439-2448 (2007)
	Kisiel "Human plasma protein C: Isolation, characterization, and mechanism of activation by α -thrombin" <i>J. Clin. Invest.</i> 64:761-769 (1979)
	Knobe et al. "Probing the activation of protein C by the thrombin-thrombomodulin complex using structural analysis, site-directed mutagenesis, and computer modeling" <i>Proteins</i> 35:218-234 (1999)
	Kuliopulos et al. "Plasmin desensitization of the PAR1 thrombin receptor: Kinetics, sites of truncation, and implications for thrombolytic therapy" <i>Biochemistry</i> 38:4572-4585 (1999)
	Marlar et al. "Mechanism of action of human activated protein C, a thrombin-dependent anticoagulant enzyme" <i>Blood</i> 59:1067-1072 (1982)
	Mather et al. "The 2.8 Å crystal structure of Gla-domainless activated protein C" <i>EMBO J.</i> 15:6822-6831 (1996)
	Mesters et al. "Identification of a sequence of human activated protein C (residues 390-404) essential for its anticoagulant activity" <i>J. Biol. Chem.</i> 266:24514-24519 (1991)
	Mosnier & Griffin "Inhibition of staurosporine-induced apoptosis of endothelial cells by activated protein C requires protease-activated receptor-1 and endothelial cell protein C receptor" <i>Biochem J.</i> 373:65-70 (2003)
	Mosnier et al. "Activated protein C variants with normal cytoprotective but reduced anticoagulant activity" <i>Blood</i> 104:1740-1744 (2004)
	Mosnier & Griffin "Protein C anticoagulant activity in relation to anti-inflammatory and anti-apoptotic activities" <i>Frontiers Biosci.</i> 11:2381-2399 (2006)
	Mosnier et al. "The cytoprotective protein C pathway" <i>Blood</i> 109:3161-3172 (2007)
	Mosnier et al. "Activated protein C mutant with minimal anticoagulant activity, normal cytoprotective activity, and preservation of thrombin activable fibrinolysis inhibitor-dependent cytoprotective functions" <i>J. Biol. Chem.</i> 282:33022-33033 (2007)
	Nicolaes et al. "Peptide bond cleavages and loss of functional activity during inactivation of factor Va and factor VaR506Q by activated protein C" <i>J. Biol. Chem.</i> 270:21158-21166 (1995)
	Norstrom et al. "Importance of protein S and phospholipid for activated protein C-mediated cleavages in factor Va" <i>J. Biol. Chem.</i> 278:24904-24911 (2003)

*Examiner

Date Considered

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GROUP

1649

OTHER DOCUMENTS (including Author, Title, Pertinent pages, Date, etc.)

	Oganesyan et al. "The crystal structure of the endothelial protein C receptor and a bound phospholipid" <i>J. Biol. Chem.</i> 277:24851-24854 (2002)
	Regan et al. "The endothelial cell protein C receptor. Inhibition of activated protein C anticoagulant function without modulation of reaction with proteinase inhibitors" <i>J. Biol. Chem.</i> 271:17499-17503 (1996)
	Riewald et al. "Activation of endothelial cell protease activated receptor 1 by the protein C pathway" <i>Science</i> 296:1880-1882 (2002)
	Ritchie et al. "Thrombin inhibits apoptosis of monocytes and plasminogen activator inhibitor 2 (PAI-2) is not responsible for this inhibition" <i>Exp. Cell. Res.</i> 260:20-29 (2000)
	Rosing & Tans "Coagulation factor V: An old star shines again" <i>J. Thromb. Haemost.</i> 78:427-433 (1997)
	Rothbarth et al. "One single mRNA encodes the centrosomal protein CCD41 and the endothelial cell protein C receptor (EPCR)" <i>FEBS Lett.</i> 458:77-80 (1999)
	Russell "Management of sepsis" <i>New Engl. J. Med.</i> 355:1699-1713 (2006)
	Sadowski et al. "Vitamin K-dependent carboxylase. Requirements of the rat liver microsomal enzyme system" <i>J. Biol. Chem.</i> 251:2770-2776 (1976)
	Shen et al. "Involvement of Lys 62(217) and Lys 63(218) of human anticoagulant protein C in heparin stimulation of inhibition by the protein C inhibitor" <i>J. Thromb. Haemost.</i> 82:72-79 (1999)
	Shu et al. "Activated protein C suppresses tissue factor expression on U937 cells in the endothelial protein C receptor-dependent manner" <i>FEBS Lett.</i> 477:208-212 (2000)
	Singh et al. "Critical care assessment and management of acute ischemic stroke" <i>J. Vasc. Interv. Radiol.</i> 15:S21-S27 (2004)
	Smirnov et al. "A chimeric protein C containing the prothrombin Gla domain exhibits increased anticoagulant activity and altered phospholipid specificity" <i>J. Biol. Chem.</i> 273:9031-9040 (1998)
	Stearns-Kurosawa et al. "The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex" <i>Proc. Natl. Acad. Sci. USA</i> 93:10212-10216 (1996)
	Taylor et al. "The endothelial cell protein C receptor aids in host defense against <i>Escherichia coli</i> sepsis" <i>Blood</i> 95:1680-1686 (2000)
	Theofilopoulos "Systemic lupus erythematosus (SLE), Experimental models" <i>Encyclopedia of Immunology</i> (Roitt & Delves, eds.) Academic Press, pp. 1414-1417 (1992)
	Thiyagarajan et al. "Activated protein C promotes neovascularization and neurogenesis in postischemic brain via protease-activated receptor 1" <i>J. Neurosci.</i> 28:12788-12797 (2008)
	UniProt: locus ROC_HUMAN, GenBank Accession No. P04070, 22 pages (1986 and updates).
	Vasserot et al. "Expanding the clinical utility of therapeutic proteins" Activated protein C variants with improved pharmacological properties" <i>Trends Pharmacol. Sci.</i> 24:501-504 (2003)
	Wang et al. "Differential neuroprotection and risk for bleeding from activated protein C with varying degrees of anticoagulant activity" <i>Stroke</i> 40:1864-1869 (2009) and doi:10.1161/STROKEAHA.108.536680 (2008)
	Warren et al. "High-dose antithrombin III in severe sepsis: A randomized controlled trial" <i>J. Am. Med. Assoc.</i> 286:1869-1878 (2001)
	Weiss et al. "Rapid mapping of protein functional epitopes by combinatorial alanine scanning" <i>Proc. Natl. Acad. Sci. USA</i> 97:8950-8954 (2000)
	Yan et al. "Characterization and novel purification of recombinant human protein C from three mammalian cell lines" <i>Biotechnol.</i> 8:655-661 (1990)
	Yednock et al. "Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha 4\beta 1$ integrin" <i>Nature</i> 356:63-66 (1992)
	Zlokovic et al. "Functional recovery after embolic stroke in rodents by activated protein C" <i>Ann. Neurol.</i> 58:474-477 (2005)

*Examiner

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